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Genital powder exposure and the risk of epithelial ovarian cancer

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Abstract
Background We conducted a population-based, case–control study to examine the association between the use of genital powder and ovarian cancer risk, including measures of extent and timing of exposure. We also assessed the relationship of powder use with risk of disease subtypes according to histology and degree of malignancy.
Methods Information was collected during in-person interviews with 812 women with epithelial ovarian cancer diagnosed in western Washington State from 2002 to 2005 and 1,313 controls. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).
Results Overall, the perineal use of powder after bathing was associated with a slightly increased ovarian cancer risk (OR = 1.27, 95% CI: 0.97–1.66), which was most evident among women with borderline tumors (OR = 1.55, 95% CI: 1.02–2.37). We noted no clear pattern of risk increase on the basis of the extent of use, assessed as years in which powder was used, or as lifetime number of applications for invasive or borderline tumors, or their histologic subtypes. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure (e.g., on sanitary napkins or diaphragms).
Conclusions The International Agency for Research on Cancer has designated perineal exposure to talc (via the application of genital powders) as a possible carcinogen in women. A modest association of ovarian cancer with this exposure was seen in our study and in some previous ones, but that association generally has not been consistent within or among studies. Therefore, no stronger adjective than "possible" appears warranted at this time.

Keywords Ovarian neoplasms · Talc · Epidemiology

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Introduction

Talc deposition in the body can lead to inflammatory and neoplastic changes [1], and perineal exposure to certain particulates (conceivably, talc) can lead to their deposition in the peritoneal cavity and ovaries [2]. Multiple case–control studies [3–5] and one cohort study [6] have examined risk of ovarian cancer associated with perineal exposure to dusting powders (many of which contain talc), either overall or within specific histologic subgroups of disease. In a meta-analysis of 20 case–control studies [3], the summary estimate of the relative risk (RR) of ovarian cancer among women who reported any perineal use of powder was 1.35 (95% confidence interval (CI): 1.26–1.46). Although no association of this exposure with ovarian cancer risk was noted in the cohort study overall, risk of invasive serous cancers was modestly elevated (by 40%). The International Agency for Research on Cancer has classified perineal exposure to talc as group 2B (possibly carcinogenic to humans [3, 7]).

In this article, we describe the results of a large population-based study of epithelial ovarian cancer conducted in western Washington State in which we further investigated the association between the use of genital powder and the

ovarian cancer risk, including measures of extent of use and aspects of timing of exposure. We also assessed the relationship of powder use with risk of disease subtypes according to histology and degree of malignancy.

Materials and methods

The study population and methods have been described previously [8]. Female residents, of a 13 county areas of western Washington State, 35–74 years of age, who were diagnosed with a primary invasive or borderline (also known as low malignant potential or LMP) epithelial ovarian tumor between 1 January 2002 and 31 December 2005, were considered eligible as cases. The cases were identified through a population-based cancer registry, the Cancer Surveillance System, which is part of the Surveillance, Epidemiology, and End Results Program (SEER) of the US National Cancer Institute. We restricted our cases to English-speaking women who had residential telephones at the time of diagnosis, because random digit dialing (RDD) was the method used to select control subjects. Of the 1,058 eligible women identified, 812 (76.6%) were interviewed. Of the interviewed cases, 595 had invasive disease. Tumors were categorized into the following histologic subgroups: serous ($n = 452$), mucinous ($n = 112$), endometrioid ($n = 104$), clear cell ($n = 35$), and other epithelial tumors ($n = 109$).

Controls were selected by RDD using stratified sampling in 5-year age categories, 1-year calendar intervals, and two county strata in a 2:1 ratio to women with invasive cancer. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to residences, we determined whether an eligible woman (i.e., an age and county eligible woman able to communicate in English and, if so, with at least one ovary and no prior history of ovarian cancer) resided there. Of the 1,561 eligible women identified, 1,313 were interviewed (84.1%) for an overall (screening X interview) response proportion of 69%.

The study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center and the University of Illinois at Urbana Champaign, and all women provided signed informed consent before participating. In-person interviews pertained to the period of time before diagnosis (for cases) or before an assigned comparable reference date (for controls), and covered the following: demographic and lifestyle characteristics; medical history; and detailed reproductive history, including menstrual, pregnancy, and contraceptive history, as well as the use of contraceptive and menopausal hormone preparations. To aid recall, interviewers used a calendar to record major life events and provided photographs of the commonly used oral contraceptive and menopausal hormone preparations.

Several sources of genital powder exposure were assessed in separate questions, including direct perineal application after bathing, its use on sanitary napkins and contraceptive diaphragms, and the use of feminine (vaginal) deodorant spray. For powder use on sanitary napkins and use of feminine deodorant sprays, we recorded the total number of months or years in which these products were used (with a minimum of at least 1 month of regular use). For the use of powder on the perineum after bathing, only intervals of at least 1 year when powder was usually used were recorded. For each reported interval in which powder was usually used on the perineum after bathing, we recorded the age when began and ended, the number of weeks or months of use per year, and the average days per week used. Women were also asked to report the types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of exposure to perineal powder after bathing was assessed as lifetime duration of use (i.e., total number of years in which this exposure occurred), and as the estimated lifetime number of applications (i.e., a measure that incorporated both the duration and frequency of use).

Using unconditional logistic regression, we calculated odds ratios (ORs) and related 95% confidence intervals (CIs) as estimates of the RR of epithelial ovarian cancer associated with various aspects of genital powder use. All the analyses were adjusted for the frequency-matching variables of age (5-year intervals), county of residence (dichotomized as the three urban or the 10 rural/suburban counties in the study), and calendar year of diagnosis/reference date (continuous), as well as number of full-term pregnancies (0, 1, 2, or ≥ 3) ,and duration of hormonal contraception (Never, <6, 6–59, 60–119, or ≥ 120 months). Additional adjustment for other potential confounding variables, including race/ethnicity, education, age at menarche, body mass index (BMI), smoking, alcohol drinking, family history of breast or ovarian cancer, personal history of breast cancer, endometriosis, tubal ligation, hysterectomy, unilateral oophorectomy, and the use of menopausal hormone therapy, produced no important change in the OR estimates. We used polytomous logistic regression to examine risk among subgroups of case women with borderline and invasive tumors and in women with different histologic subtypes of these tumors. Because we had limited facility to separately examine risk of mucinous invasive ovarian cancer owing to its rarity ($n = 23$), we excluded these tumors when examining histologic subtypes of invasive disease; similarly, we limited our examination of histologic subtypes of borderline tumors to serous or mucinous subtypes (excluding 11 women with other, uncommon histologic subtypes of borderline tumors). All the analyses were carried out using the STATA version 10 statistical package (Statacorp LP, College Station, Texas).

Results

Characteristics of cases and controls have previously been described [8, 9]. Approximately 90% of cases and controls were non-Hispanic white women. Cases were less likely than controls to have given birth, and reported a lesser extent of exposure to hormonal forms of contraception. Cases were somewhat more likely than controls to be overweight (BMI 25–<30 kg/m^2) or obese (BMI ≥ 30 kg/m^2), and less likely to have graduated from college (results not shown).

The use of powder after bathing (for at least 1 year of regular use, as described above) was reported by approximately 12% of controls (Table 1). Other sources of powder exposure (e.g., on sanitary napkins) and the use of deodorant sprays were reported by a slightly smaller proportion of women, despite the shorter minimum time interval allowed in our assessment of these exposures (see Methods for description). Overall, the perineal use of powder after bathing was associated with a slightly increased risk (OR = 1.27, 95% CI: 0.97–1.66), which was the most evident among women with borderline tumors (OR = 1.55, 95% CI: 1.02–2.37). No clear elevation in risk of borderline or invasive tumors were observed in association with the use of powders on sanitary napkins or contraceptive diaphragms, or with the use of feminine deodorant sprays (Table 1). The most frequently reported category of product used after bathing was baby powder (not shown); few women reported exclusive use of talcum powder or of cornstarch (a product that does not contain talcum powder). Within limits of precision, findings regarding ovarian cancer risk among women who reported the use of talcum powder were similar to those presented for all types of powders combined; e.g., the risk of invasive ovarian cancer among women who reported the use of talcum powder was 1.38 (95% CI: 0.77–2.47).

We noted no evidence that risk of ovarian cancer increased in association with increasing extent of the use of perineal dusting powder (assessed as years in which powder was used or as lifetime number of applications) for either invasive or borderline tumors (Table 2). Similarly, we observed no trend in risk with increasing years of powder use on sanitary napkins or with the use of feminine deodorant sprays (results not shown). Risk (relative to never-users) was increased among women who first reported the regular use of perineal dusting powders at age 30 years or older (OR for invasive and borderline tumors combined = 1.69, 95% CI: 1.08–2.64), among women whose first regular use was in 1980 or later (OR for invasive and borderline tumors combined = 2.03, 95% CI: 1.28–3.24), and among women who had initiated regular use within the last 25 years (cut-off point based on approximate quartiles of exposed controls; OR for invasive and borderline tumors combined = 1.77, 95% CI: 1.12–2.78). Point estimates for each of these exposure subgroups were similar for borderline and invasive tumors (Table 2).

We repeated our analyses after [1] restricting the analysis to the use of perineal powder that occurred before tubal ligation and/or hysterectomy (for women who had undergone those procedures) and [2] restricting it to the use of

Table 1 Risk of epithelial ovarian cancer in relation to various sources of genital powder exposure overall and among women with borderline and invasive tumors

	Controls	Borderline tumors			Invasive tumors			All tumors		
	(n = 1,313)[a]	(n = 217)[a]	OR[b]	95% CI	(n = 595)[a]	OR[b]	95% CI	(n = 812)[a]	OR[b]	95% CI
Used powder after bathing										
No	1,161	184	1.00	Ref.	515	1.00	Ref.	699	1.00	Ref.
Yes	151	33	1.55	1.02–2.37	79	1.17	0.87–1.58	112	1.27	0.97–1.66
Used powder on sanitary napkins										
No	1,197	201	1.00	Ref.	552	1.00	Ref.	753	1.00	Ref.
Yes	109	16	1.03	0.58–1.84	39	0.75	0.51–1.12	55	0.82	0.58–1.16
Used powder on diaphragm[c]										
No	321	44	1.00	Ref.	116	1.00	Ref.	160	1.00	Ref.
Yes	121	9	0.60	0.27–1.33	37	0.77	0.49–1.21	46	0.72	0.48–1.10
Used vaginal deodorant spray										
No	1,185	194	1.00	Ref.	532	1.00	Ref.	726	1.00	Ref.
Yes	125	23	1.20	0.74–1.95	61	1.14	0.81–1.59	84	1.15	0.85–1.56

[a] Numbers in column may not sum to total due to missing values

[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full-term births, and duration of hormonal contraception

[c] Restricted to diaphragm users

Table 2 Risk of epithelial ovarian cancer in relation to the use of perineal powder after bathing by duration and timing of use, overall and among women with borderline and invasive tumors

	Controls	Borderline tumors			Invasive tumors			All tumors		
	(n = 1,313)[a]	(n = 217)[a]	OR[b]	95% CI	(n = 595)[a]	OR[b]	95% CI	(n = 812)[a]	OR[b]	95% CI
Never used[c]	1,161	184	1.00	Ref.	515	1.0	Ref.	699	1.0	Ref.
Duration of use (years)										
1–9.9	38	9	1.33	0.61–2.87	24	1.42	0.83–2.43	33	1.39	0.85–2.28
10–19.9	35	10	1.97	0.93–4.17	19	1.28	0.71–2.29	29	1.46	0.87–2.45
20–34.9	40	10	1.83	0.88–3.80	20	1.11	0.63–1.95	30	1.28	0.78–2.10
35+	38	4	1.08	0.37–3.15	15	0.86	0.46–1.60	19	0.91	0.51–1.62
Lifetime number of applications										
1–1,599	36	6	1.05	0.42–2.61	20	1.26	0.71–2.25	26	1.21	0.71–2.06
1,600–4,799	37	17	3.11	1.67–5.78	28	1.72	1.03–2.88	45	2.08	1.32–3.27
4,800–9,999	39	6	1.19	0.49–2.92	14	0.78	0.41–1.48	20	0.87	0.50–1.53
10,000+	37	4	0.98	0.34–2.85	14	0.84	0.44–1.59	18	0.87	0.48–1.57
Age at first use (years)[c]										
<15	27	4	0.89	0.30–2.66	8	0.67	0.30–1.53	12	0.74	0.37–1.50
15–<20	36	8	1.46	0.64–3.31	19	1.10	0.61–1.97	27	1.20	0.71–2.03
20–<30	43	12	1.93	0.98–3.80	20	1.04	0.59–1.81	32	1.25	0.77–2.03
30+	45	9	1.68	0.79–3.60	32	1.68	1.04–2.72	41	1.69	1.08–2.64
Age at last use (years)[c]										
<35	33	10	1.54	0.72–3.28	15	0.97	0.51–1.83	25	1.14	0.66–1.97
35–<50	39	15	2.07	1.09–3.93	20	1.15	0.65–2.03	35	1.42	0.88–2.31
50–<60	36	6	1.39	0.56–3.44	19	1.20	0.67–2.15	25	1.25	0.73–2.13
60+	43	2	0.64	0.15–2.74	24	1.30	0.76–2.25	26	1.21	0.72–2.05
Calendar year of first use[c]										
≤1959	39	5	1.47	0.55–3.92	14	0.73	0.38–1.40	19	0.86	0.48–1.53
1960–1969	38	4	0.82	0.28–2.38	20	1.18	0.66–2.09	24	1.10	0.65–1.89
1970–1979	38	11	1.65	0.81–3.37	15	0.91	0.49–1.69	26	1.12	0.66–1.89
1980+	36	33	2.20	1.11–4.34	30	1.97	1.18–3.28	43	2.03	1.28–3.24
Time since first use (years)[c]										
≤25	41	12	1.78	0.89–3.54	30	1.76	1.07–2.89	42	1.77	1.12–2.78
25–<38	41	14	1.98	1.03–3.79	24	1.25	0.73–2.13	38	1.46	0.91–2.32
38–<45	34	3	0.79	0.23–2.69	13	0.88	0.45–1.72	16	0.87	0.47–1.61
45+	35	4	1.30	0.44–3.83	12	0.72	0.36–1.43	16	0.82	0.44–1.52
Time since last use (years)[c]										
Current user	70	12	1.35	0.71–2.59	40	1.28	0.85–1.94	52	1.30	0.89–1.91
≤12	26	9	2.11	0.94–4.77	17	1.59	0.83–3.02	26	1.74	0.98–3.10
13–23	27	7	1.80	0.75–4.34	7	0.55	0.24–1.29	14	0.85	0.44–1.66
24+	28	5	1.22	0.45–3.29	14	1.10	0.56–2.17	19	1.13	0.61–2.08

[a] Numbers in column may not sum to total due to missing values

[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full-term births, and duration of hormonal contraception

[c] Use defined as regular use after bathing for at least 1 year

powder that occurred at age 15 years or later. Results were generally similar to those that we have presented. Associations with any perineal powder exposure that occurred in women with intact fallopian tubes were slightly reduced in comparison to analyses that included powder use irrespective of the occurrence of tubal ligation or hysterectomy (e.g., ORs among women with intact tubes = 1.23 [95% CI: 0.93–1.64] and 1.44 [95% CI: 0.92–2.24], for all ovarian tumors combined and for borderline tumors, respectively). Associations with any perineal powder used

Table 3 Risk of histologic types of invasive and borderline epithelial ovarian cancer in relation to various sources of genital powder

	Borderline tumors[c]				Invasive tumors[c]					
	Mucinous (n = 89)		Serous (n = 117)		Serous (n = 335)		Endometrioid/Clear (n = 133)		Other nonmucinous (n = 104)	
	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)	N	OR[a] (95% CI)
Used powder after bathing[b]										
No	74	1.0 (Ref.)	100	1.0 (Ref.)	295	1.0 (Ref.)	112	1.0 (Ref.)	87	1.0 (Ref.)
Yes	15	1.78 (0.98–3.23)	17	1.47 (0.84–2.55)	40	1.01 (0.69–1.47)	21	1.53 (0.91–2.57)	17	1.48 (0.85–2.58)
Duration of use[b] (years)										
1–9.9	2	0.71 (0.16–3.10)	7	1.89 (0.80–4.47)	11	1.16 (0.58–2.33)	6	1.42 (0.56–3.57)	6	2.18 (0.88–5.40)
10–19.9	6	3.12 (1.22–7.97)	3	1.10 (0.33–3.70)	11	1.26 (0.62–2.54)	5	1.62 (0.60–4.41)	3	1.16 (0.35–3.92)
20–34.9	5	2.45 (0.92–6.56)	5	1.60 (0.60–4.22)	8	0.76 (0.35–1.66)	5	1.40 (0.52–3.74)	7	2.25 (0.97–5.24)
35+	2	1.26 (0.29–5.51)	2	1.02 (0.24–4.40)	10	0.91 (0.44–1.88)	5	1.85 (0.68–5.05)	0	0.00 (–)
Age at first use (years)[b]										
<15	1	0.56 (0.07–4.27)	3	1.24 (0.36–4.30)	3	0.44 (0.13–1.47)	3	1.20 (0.34–4.24)	2	1.02 (0.23–4.43)
15–<20	5	2.30 (0.84–6.33)	3	1.01 (0.30–3.43)	10	1.01 (0.49–2.08)	7	1.99 (0.83–4.76)	2	0.63 (0.15–2.72)
20–<30	5	2.14 (0.80–5.68)	6	1.69 (0.69–4.15)	10	0.90 (0.44–1.83)	3	0.68 (0.20–2.31)	6	1.82 (0.74–4.47)
30+	4	1.80 (0.61–5.28)	5	1.77 (0.67–4.66)	17	1.45 (0.81–2.59)	8	2.33 (1.03–5.27)	7	2.21 (0.95–5.11)
Calendar year of first use[b]										
≤1959	3	2.08 (0.59–7.30)	2	1.07 (0.25–4.70)	6	0.50 (0.20–1.20)	5	1.78 (0.64–4.95)	3	0.89 (0.26–3.03)
1960–1969	4	2.12 (0.71–6.32)	0	0.00 (–)	12	1.18 (0.60–2.33)	5	1.38 (0.51–3.76)	2	0.72 (0.17–3.08)
1970–1979	3	1.21 (0.36–4.10)	7	1.94 (0.82–4.57)	6	0.66 (0.27–1.60)	5	1.34 (0.50–3.60)	4	1.38 (0.47–4.06)
1980+	5	2.05 (0.76–5.55)	8	2.50 (1.10–5.64)	16	1.84 (1.00–3.40)	6	1.75 (0.70–4.40)	8	3.07 (1.37–6.88)
Time since first use (years)[b]										
≤25	5	1.79 (0.67–4.82)	7	1.93 (0.83–4.52)	16	1.65 (0.90–3.00)	6	1.58 (0.63–3.93)	8	2.73 (1.22–6.07)
26–<38	5	1.89 (0.71–5.06)	8	2.09 (0.93–4.69)	11	1.05 (0.53–2.10)	8	1.80 (0.79–4.08)	5	1.51 (0.57–4.00)
38–<45	3	2.14 (0.61–7.47)	0	0.00 (–)	7	0.75 (0.33–1.75)	4	1.45 (0.48–4.38)	1	0.41 (0.05–3.07)
45+	2	1.46 (0.33–6.49)	2	1.22 (0.28–5.38)	6	0.56 (0.23–1.37)	3	1.19 (0.34–4.19)	3	1.02 (0.30–3.52)

[a] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception

[b] Use defined as regular use after bathing for at least 1 year

[c] Not included are 6 endometrioid borderline, 5 other borderline, and 23 mucinous invasive tumors

≥15 years of age were slightly stronger (e.g., ORs among such women = 1.30 [95% CI: 0.99–1.71] and 1.63 [95% CI: 1.07–2.49], for all ovarian tumors combined and for borderline tumors, respectively).

Risk of mucinous borderline tumors was particularly elevated among women who reported any regular use of perineal dusting powder (OR = 1.78, 95% CI: 0.98–3.23), with a lesser risk increase for serous borderline tumors (Table 3). We observed no association of perineal powder use with risk of serous invasive tumors (OR = 1.01, 95% CI: 0.69–1.47), and some suggestion that risk was elevated for the combined group of endometrioid and clear cell invasive tumors (OR = 1.53, 95% CI: 0.91–2.57). Similar to the overall results, we observed no association with measures of extent of the use of perineal dusting powder for any specific histologic subtype. Elevations in risk noted in our overall results among women in the most recent category of age at or time since first use and in the most recent (1980 or later) calendar period of initiation of powder use were broadly similar across histologic subtypes.

Discussion

A number of case–control studies of ovarian cancer, in addition to ours, have examined the issue of genital powder exposure as a potential risk factor. The validity of all of these studies, including ours, may be influenced by the level of non-response among cases and controls, and by the potential for misclassification (differential and non-differential) of exposure status. The latter derives not just from errors in the recall of the use of genital powder, but from the fact that the presence or concentration of talc can vary

from brand to brand and even within one brand of powder over time. Therefore, even when respondents are asked specifically about perineal exposure to powders that contain talc (as in our study), they may be unable to provide accurate information. Reporting of the use of pure cornstarch powder, however, was quite uncommon in this study; if this information is accurate (and this pattern of use extends to other populations), and if the presence, rather than concentration, of talc in dusting powder is the primary determinant of meaningful exposure, then measures of genital powder use of any type may yet serve as a reasonable surrogate for talc exposure.

In support of an inference that genital exposure to powders has the capacity to cause ovarian cancer is the observation of a 30–60% increase in risk across most case–control studies [3]; in this regard, our findings are similar to prior studies. However, a non-causal interpretation may be consistent with the absence of an overall association in the one cohort study of the question [6], along with the absence in most studies (including the current study) of a trend of increasing risk with increasing duration of exposure [3]. However, ovarian talc particle burden has been found not to correlate with the reported number of lifetime applications [10], which (if not reflective of inaccurate reporting) may indicate that duration of the powder use is not relevant when assessing risk associated with differing levels of exposure to talc.

While the increased risk that we observed was largely restricted to borderline tumors, some studies have reported results either similar to [e.g., 11] or different from [e.g., 5, 12] these latter findings. Also, our results add further inconsistency to the results regarding the strength of association of the perineal powder use with histologic subtypes of disease. In particular, we noted no increase in risk of serous invasive disease, in contrast to some [e.g., 4–6] studies—including the single cohort study [6]—that reported the strongest associations with that subtype. Analyses aimed at examining perineal powder during specific time intervals—whether by calendar year, recency of use, or life intervals in which constituents of perineal powder might ascend through the reproductive tract unimpeded by, e.g., closure of the fallopian tubes—either failed to sharpen exposure–disease relationships or yielded results opposite to those that had been observed or hypothesized by others. For example, Wu et al. [5] observed higher risks among women who initiated talc use before 1975, consistent with the hypothesis that products in use before that year were more likely to be carcinogenic owing to contamination with asbestos fibers; in contrast, we noted stronger associations among women who had only used perineal powder during or after 1980.

It is not evident how (or if) additional investigation will be able to resolve the issue of whether perineal exposure to talc predisposes to ovarian malignancy. Further case–control studies will continue to be hindered by the limitations mentioned above. Data from additional cohort studies would be welcome, but without details concerning the composition of the powders used by cohort members—details that many participants may not be able to provide—the results of such studies may similarly be ambiguous in their interpretation.

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